L4: Entry 21 of 44 File: USPT May 23, 2000

DOCUMENT-IDENTIFIER: US 6066331 A
TITLE: Method for preparation of vesicles loaded with biological structures, biopolymers and/or oligomers

Brief Summary Text (3):
Grey, A. and Morgan, J. report that liposomes were first described nearly a quarter of a century ago and have been useful models for studying the physical chemistry of lipid bilayers and the biology of the cell membrane. It was also realised that they might be used as vehicles for the delivery of drugs but clinical application have been slow to emerge. Proposed clinical uses have included vaccine adjuvancy, gene Transfer and diagnostic imaging but the major effort has been in the development of liposomes as targetable drug carriers in the treatment of malignancy. Although based on good in vitro data and animal studies, the strategies have been mostly impractical due to the predominant but unwanted uptake by the reticuloendothelial system and the limited extent of extravasation. The same features have nonetheless been turned to advantage in the case of amphotericin B which has recently become the first liposomally formulated agent to be licensed for parenteral use. Liposomal doxorubicin is currently also being evaluated in clinical trials. The early evidence suggests that while liposomal encapsulation may not greatly enhance their efficacy the toxicity of these agents is greatly attenuated (A. Gray, J. Morgan, "Liposomes in Haematology" in Blood Reviews, 1991, 5, 258-271).

Brief Summary Text (4):
Liposomes have been used in biological systems such as plasma extravascular space like reticuloendothelial system to more access celluar uptake of liposomes. Liposomes were loaded with amphotericin which is an effective but toxic antifungal. Antitumor agents like adriamycine have also be incorporated into liposomes. Vaccines and adjuvants as well as biological response modifiers like lymphocines and so on were studyed in encapsulated form. Liposomes are discussed in field of a gene transfert as vehicles.

Brief Summary Text (5):
N. Sakuragawa et al. report in Thrombosis Research 38, 681-685, 1985, 1988 Clinical Hematology 29 (5) 655-661, that liposomes containing factor VIII have been prepared for oral administration to patients which are suffering from von Willebrand's disease. The encapsulation was carried out by dissolving the protein factor VIII concentrates in an aprotinin containing solution and transferred into lecithin coated flasks. After drying the flasks by rotation for 30 min under negative pressure liposomes were formed which entrapped factor VIII concentrates. The liposome solution was centrifuged yielding 40% of factor VIII entrapped in liposomes.

Brief Summary Text (6):
Another method for entrapment of drugs in liposomes is based on dehydration - rehydration. This is described by C. Kirby and G. Gregoriadis in Bio/Technology, November 1984, pages 979-984. In this preparation the entrapments can be increased by using additional lipid. Disclosed is the use of cholesterol as being of positive influence of the drug entrapment. Since cholesterol is involed in the pathobio-chemistry of some disorders, administration of cholesterol containing vesicles is not harmless at all.

Brief Summary Text (9):
Liposomes can be classified according to various parameters.

Brief Summary Text (10):
For example, when size and number of lamellae (structural parameters) are used than three major types of liposomes have been described: Multilamellar vesicles (MLV), small unilamellar vesciles (SUV) and large unilamellar vesicles (LUV). MLV are the species which form spontaneously on hydration of dried phospholipids above their gel to liquid crystalline phase transition temperature (Tm). Their size is heterogenous and their structure resembles an onion skin of alternating, concentric aqueous and lipid layers.

Brief Summary Text (12):
A third type of liposome LUV has a large aqueous compartment and a single (unilamellar) or only a few (oligolamellar) lipid layers.

Brief Summary Text (13):
Further details are disclosed in D. Lichtenberg and Y. Barenholz, Liposomes: Preparation, Characterization, and Preservation, in Methods of Biochemical Analysis, Vol. 33, pp. 337-462, as exemplified in FIG. 3.

Brief Summary Text (15):
As used herein, the term "liposome" is intended to include all spheres or vesicles of any amphiphatic compounds which may spontaneously or non-spontaneously vesiculate, for example phospholipids where at least one acyl group replaced by a complex phosphoric acid ester. The most of triacylglycerol is suitable and most common phospholipids for the present invention are the lecithines (also referred to as phosphatidylcholines (PC)), which are mixtures of the diglycerides of stearic, palmitic, and oleic acids linked to the choline ester of phosphoric acid. The lecithines are found in all animals and plants such as eggs, soybeans, and animal

Brief Summary Text (19):
The liposomes can be "tailored" to the requirements of any specific reservoir including various biological fluids, maintains their stability without aggregation or chromatographic separation, and remains well dispersed and suspended in the injected fluid. The fluidity in situ changes due to the composition, temperature, salinity, bivalent ions and presence of proteins. The liposome can be used with or without any other solvent or surfactant.

Brief Summary Text (21):
The liposomes may contain other lipid components, as long as these do not induce instability and/or aggregation and/or chromatographic separation. This can be determined by routine experimentation.

Brief Summary Text (22):
A variety of methods for producing the modified liposomes which are unilamellar or multilamellar are known and available:

Brief Summary Text (26):
4. Preparing lipid detergent mixed micelles then lowering the concentration of the detergents to a level below its critical concentration at which liposomes are formed (Lichtenberg, Barenholz, 1988).

Brief Summary Text (27):
In general, they produce liposomes with heterogeneous sizes from about 0.02 to 10 .mu.m or greater. Since liposomes which are relatively small and well defined in size are preferred for use in the present invention, a second processing step defined as "liposome down sizing" is for reducing the size and size heterogeneity of lioosome suspensions.

Brief Summary Text (28):
The liposome suspension may be sized to achieve a selective size distribution of vesicles in a size range less than about 5 .mu.m and preferably to be .ltoreq.0.4 .mu.m. Liposomes in this range can readily be sterilized by filtration through a suitable filter. Smaller vesicles also show less a tendency to aggregate on storage, thus reducing potentially serious blockage or plugging problems when the liposome is injected intravenously. Finally, liposomes which have been sized down to the submicron range show more uniform distribution.

Brief Summary Text (29):
Several techniques are available for reducing the sizes and size heterogeneity of liposomes, in a manner suitable for the present invention. Ultrasonic irradiation of a liposome suspension either by standard bath or probe sonication produces a progressive size reduction down to small unilamellar vesicles (SUVs) between 0.02 and 0.08 .mu.m in size. Homogenization is another method which relies on shearing energy to fragment large liposomes into smaller ones. In a typical homogenization procedure the liposome suspension is recirculated through a standard emulsion homogenizer until selected liposome sizes, typically between about 0.1 and 0.5 .mu.m are observed. In both methods, the particle size distribution can be monitored by conventional laser-beam particle size determination.

Brief Summary Text (30):
Extrusion of liposomes through a small-pore polycarbonate filter or equivalent membrane is also an effective method for reducing liposome sizes down to a relatively well-defined size distribution whose average is in the range between about 0.02 and 5 .mu.m, depending on the pore size of the membrane. Typically, the suspension is cycled through one or two stacked membranes several times until the desired liposome size distribution is achieved. The liposome may be extruded through successively smaller pore membranes, to achieve a gradual reduction in lipsome size.

Brief Summary Text (31):
Centrifugation and molecular sieve chromatography are other methods which are available for producing a liposome suspension with particle sizes below a selected threshold less than 1 .mu.m. These two respective methods involve preferential removal of large liposomes, rather than conversion of large particles to smaller ones. Liposome yields are correspondingly reduced.

Brief Summary Text (32):
The size-processed liposome suspension may be readily sterilized by passage through a sterilizing membrane having a particle discrimination size of about 0.4 .mu.m, such as a conventional 0.45 .mu.m depth membrane filter. The liposomes are stable in lyophilized form and can be reconstituted shortly before use by taking up in water.

Detailed Description Text (9):
It is understood the skilled person that the amount of organic polar-protic solvent miscible with water is strongly dependent on it interference with the substance to be encapsulated to the liposomes. For example, for HBsAg 50% is tolerable while factor IX (which is a clotting-factor) is to be encapsulated as an amount of approximately 30% of tert-butanol is tolerable. This may strongly vary with the nature of the substance to be encapsulated. For example, if factor IX which is a clotting factor is to be encapsulated an amount of about 30% of tertiary butanol is tolerable, whereas, factor VIII is much more sensitive to the impact of tert.-butanol. In this case an amount of less than 10% of tert.-butanol is preferred. The percentage of t-butanol in these examples is based on percent by volume calculated for final concentration.

Detailed Description Text (12):

According to the method of the invention the product obtained as described above in dry form is taken up in an aqueous medium. Thereby, liposomes formed become loaded with the respective biological structures, biopolymers and/or oligomers. The system typically forms a dispersion.

Detailed Description Text (17):
A method of treatment and/or prophylaxis of diseases by administering an effective amount of the medicament according to the invention is provided. It is understood by the skilled person that the dosage is depending on the concentration of the effective substances as well as their efficiency. According to the method of treatment and/or prophylaxis of the invention preferably a dosage of up to 2,000 mg vesicles (e. g. phospholipid liposomes)/kg body weight is administered to the patient. The accurate dosage can vary dramatically. The variation, however, depends on e. g. the type and efficacy of the substance encapsulated in the liposomes, the efficiency of the encapsulation reaction itself (being high with the method of the invention), the kind of administration and the like. The respective parameters can be easily optimized by the person skilled in the art and can be regarded as being routine experiments.

Detailed Description Text (23):
A mixture of DMPC : DMPG in a molar ratio of 9:1 respectively was prepared in tert.-butanol. An aqueous HBsAg solution such as 0.9% NaCl in 1:1 (v/v) was added. The final HBsAg: phospholipids (w/w) ratio was 0.0015. The solution was frozen and dried by lyophilisation. A dry powder was obtained which was reconstituted before use with double distilled sterile pyrogen-free water. Multilamellar liposomes were formed; loading efficiency of HBsAg was 97%. "Empty liposomes" were prepared similarly by mixing 1 vol of aqueous solution of 0.9%. NaCl with 1 vol of lipid solution in tertiary butanol.

Detailed Description Text (24):
The extent of HBsAg exposure on the liposome surface of sample 1 and liposome size was determined. It was found that the size of these lipsomes was 4.5 .mu.m and the exposure of the antigen on the liposome surface was tested. It was found that the titer of antibodies which was developed was high and sufficient to protect against infection by HBV (see Table 1). The titer was similar to that obtained in mice that were vaccinated with the same antigen using aluminum hydroxide based vaccine except for the high dose of injected antigen (2.5 .mu.g) in which the liposomal vaccine was inferior: injection of this dose to mice in the control group stimulated the highest titer of antibodies.

Detailed Description Text (26):
Liposomes loaded with HBsAg and "empty liposomes" were prepared as described for sample 1. A group of seven Balb/c mice, six weeks old, were vaccinated by 0.09 g HBsAg loaded in liposomes which were diluted with "empty liposomes" and 0.9% NaCl. The final injection volume was 0.5 ml/mice, which included also 1 mg/kg mice of the immunomodulator MTP-PE in POPC/DOPS (7:3 mole ratio) liposomes. After 35 days the level of anti-HBs in the mice was measured. The titer of antibodies was twice the titer which developed after injecting the same dose of antigen without MTP-PE

Detailed Description Text (29):
Liposomes loaded with HBsAg and identical "empty liposomes" were prepared as described for sample 1 with one difference in that the aqueous solution used for lipid hydration also contained 5% lactose. The liposomes were frozen and dried. A powder was obtained which was reconstituted before use with sterile pyrogen-free bidistilled water. The liposomes were characterized for their size, percentage of antigen loading and the extent of antigen exposure on the liposome surface. The immunization efficacy of the preparation was tested in Balb/c mice, six weeks old. The mice were divided into three groups, five mice in each group, and the animals were vaccinated using three doses of antigen: 0.09 .mu.g, 0.27 .mu.g, 0.81 .mu.g, respectively. Anti-HBs was measured after 35 days (see Table 1). A high titer of

antibodies was observed which should be sufficient to protect against HBV infection.

Detailed Description Text (32):
Liopsomes loaded with HBsAg were prepared as described for sample 3. Three groups of five Balb/c mice, six weeks old, were vaccinated with four doses of HBsAg at a level of 0.09 .mu.g, 0.27 .mu.g, 0.81 .mu.g, respectively. The total injection volume was 0.5 ml/mice. The liposomes were diluted with PBS only and not with "empty liposomes" and therefore the amount of lipid varied and increased with increasing protein level. After 35 days the mice were bled and their serum antibody titer was determined. The results show a high titer of antibodies which should be sufficient to protect against infection by HBV.

Detailed Description Text (50):
Preparation and Characterization of Factor-IX-Loaded Liposomes

Detailed Description Text (51):
Two different methods of liposome preparation will be compared for stability and Factor IX encapsulation.

Detailed Description Text (55):
Preparation of multilamellar vesicles loaded with Factor-IX by the DRV method require the following steps: preparation of small unilamellar vesicles (SUV's) in bidistilled water, mixing them with a solution of factor IX previously dialyzed against amino acids and flash-frozen the mixture. After lyophilization, multilamellar vesicles loaded with Factor-IX were obtained by rehydrating the preparation with bidistilled water, then stepwise saline is added, until the final liposomes concentration was reached. At this point the multi-lamellar vesicles can be sized by extrusion to obtain oligo-lamellar or small unilamellar vesicles.

Detailed Description Text (56):
Rehydration of lyophilized material with minimal volume results in an increase of the overall concentration of the factor. After liposomes are formed the solution can be further diluted without affecting the loading efficiency, and this is reflected in the concentration of the material that is actually loaded. Since liposomes are osmotically active, losses of material on exposure to hypotonic media during all manipulations subsequent to hydrating were minimzed by dialyzing the Factor before mixing with the SUV's to obtain a lower osmolarity in the liposome interior during the rehydration step.

Detailed Description Text (58):
In this preparation lipid solubilized in tert-butanol is mixed with an aqueous solution of the factor to obtain an homogeneous solution. The solution is frozen and the solvent removed by lyophilization. Mulitlamellar vesicles loaded with Factor-IX are obtained by hydration of the dry mixture, firstly in small volume of bidistilled water, then stepwise with saline, until the final liposome concentration is reached. At this point the multlamellar vesicles can be sized by extrusion to obtain oligolamellar or small unilamellar vesicles.

Detailed Description Text (62):
Liposomes containing factor IX were pelleted by centrifugation in an Eppendorff centrifuge at 12,000 g for 10 min and the factor IX activitiy was determined in the supernatants and pellet. The pellet was solubilized prior analysis with Triton X-100. A concentration dependency on factor IX activity with Triton X100 was found. 1% Triton X100 (final concentration) caused a 50% loss of activity, while no loss was observed at 0.2%. In general, the total activity of the factor was recuperated, namely, the activity of the super-natants and pellet was always similar or even higher than the inital activity of the preparation. The loading efficiency was higher than 80%.

Detailed Description Text (66):
A mixture of DMPC:DMPG in a molar ratio of 9:1 respectively was dissolved in tert-butanol in a 1:6.7 w/v ratio. The mixture was heated and stirred until the lipids were dissolved. After sterile filtration, sterile water was added to the organic mixture until a 1: 1 (v/v) ratio between the tert-butanol and the water was reached. An aqueous solution of the melanomic membrane mixture was added to a 1:750 protein : phospholipids (w/w) ratio. This final mixture was divided in single doses of 1 g phospholipids and each one was frozen and dried by lyophilization. A dry powder was obtained and stored at -70.degree. C. Prior to application liposomes were formed by rehydration in double distilled, sterile and pyrogen-free aqueous solution containing 0.9% NaCl to obtain a liposome dispersion of 10% phospholipid concentration. After reconstitution, this liposomes had an average size of 1 .mu.m and an average phospholipid: protein ratio of 765:1.

Detailed Description Text (78):
Vaccine in liposomes

Detailed Description Text (91):
(2) Membranes were loaded in liposomes consisting of DMPC: DMPG in a 9:1 molar ratio, were tested for sterility, pyrogenicity and tumorigenicity in nude mice;.

Detailed Description Text (101):
DMPC: DMPG at a 9:1 molar ratio were dissolved in tert-butanol in a 1:10 (w:v) ratio and the lipid mixture was pre-warmed to dissolve the lipids completely. An aqueous ribosomal mixture containing 1.5 mg ribosomes/ml (determined by Orcinol) was added to the lipids at a 1:100 w/w final ratio. In some cases Lipid-A was added at this stage as an adjuvant in a 1:1,000 lipid-A to phospholipids molar ratio. This suspension was frozen and lyophilized in aliquouts of 0.5 g phospholipids and the dry powder was stored at -20.degree. C. Prior application liposomes were formed by adding two aliquots of 0.5 ml volume of double distilled, sterile and pyrogen free aqueous solution containing 0.9% NaCl.

Detailed Description Text (106):
Group 3: liposomes containing ribosomes

Detailed Description Text (107):
Group 4: liposomes containing ribosomes and lipid-A.

Detailed Description Text (110):
Preparation of Liposomes Containing Anti-haemophilic Factor IX

Detailed Description Text (111):
Liposomes Preparation

Detailed Description Text (112):
Purified egg yolk phosphatidylcholine was dissolved in tert-butanol at various ratios and the mixture was slightly warmed until the phospholipid was dissolved. Double distilled sterile, pyrogen free water was added until the desired ratio between the organic solvent and the water was reached. An aqueous solution of salt free Factor IX (OCTANYNE.RTM. adjusted pH 7.4 was added to the suspension under continuous mixing and subsequently lyophilized. The ratio of the total protein to phospholipid was 1:400 (w/w). The dry mixture was stored at 40.degree. C. Liposomes of 1 .mu.m average size were prepared by hydrating the powder with aliquots of sterile, pyrogen-free double distilled water and mixing well between the additions. The last addition consisted of saline to raise the salt concentration to isosmotic conditions.

Current US Original Classification (1):
424/450

Current US Cross Reference Classification (1):
424/520

Current US Cross Reference Classification (2):
424/93.7

Current US Cross Reference Classification (3):
424/94.1

CLAIMS:

10. The method of claim 2 further comprising the step of hydrating the dry product in an aqueous medium to form liposomes.

20. The liposomes made by the method of claim 10.

23. A medicament comprising the liposomes of claim 20 in combination with a pharmaceutically acceptable vehicle.

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☐ 31. Document ID: US 5767246 A

L4: Entry 31 of 44 File: USPT Jun 16, 1998

US-PAT-NO: 5767246
DOCUMENT-IDENTIFIER: US 5767246 A

TITLE: Human monoclonal antibody specifically binding to surface antigen of cancer cell membrane

DATE-ISSUED: June 16, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hosokawa; Saiko	Kawasaki			JP
Tagawa; Toshiaki	Yokohama			JP
Hirakawa; Yoko	Yokohama			JP
Ito; Norihiko	Yokohama			JP
Nagaike; Kazuhiro	Sagamihara			JP

US-CL-CURRENT: 530/388.8; 424/138.1, 424/142.1, 424/155.1, 424/174.1, 435/330, 435/344, 435/372.2, 530/387.7, 530/388.15 , 530/389.7, 530/865, 530/866, 530/867, 536/23.53

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 32. Document ID: US 5707643 A

L4: Entry 32 of 44 File: USPT Jan 13, 1998

US-PAT-NO: 5707643
DOCUMENT-IDENTIFIER: US 5707643 A

TITLE: Biodegradable scleral plug

DATE-ISSUED: January 13, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ogura; Yuichiro	Kyoto			JP
Ikada; Yoshito	Uji			JP

US-CL-CURRENT: 424/428; 424/426, 424/427

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 33. Document ID: US 5700482 A

L4: Entry 33 of 44 File: USPT Dec 23, 1997

US-PAT-NO: 5700482
DOCUMENT-IDENTIFIER: US 5700482 A

TITLE: Process for the preparation of a liposome dispersion under elevated pressure contents

DATE-ISSUED: December 23, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Frederiksen; Lene	Basel			CH
Anton; Klaus	Basel			CH
van Hoogevest; Peter	Riehen			CH

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 34. Document ID: US 5695738 A

L4: Entry 34 of 44 File: USPT Dec 9, 1997

US-PAT-NO: 5695738
DOCUMENT-IDENTIFIER: US 5695738 A

TITLE: Steroidal C-glycosides

DATE-ISSUED: December 9, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Anderson; Mark	Orinda	CA		
Musser; John Henry	San Carlos	CA		

US-CL-CURRENT: 424/1.73; 424/9.1, 514/25, 514/359, 514/461, 536/5, 536/6, 536/6.1, 536/6.2, 540/95, 540/97, 540/99

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 35. Document ID: US 5676971 A

L4: Entry 35 of 44 File: USPT Oct 14, 1997

US-PAT-NO: 5676971
DOCUMENT-IDENTIFIER: US 5676971 A
** See image for Certificate of Correction **

TITLE: Agents for inhibiting adsorption of proteins on the liposome surface

DATE-ISSUED: October 14, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yoshioka; Hiroshi	Shizuoka-ken			JP
Goto; Hiroshi	Shizuoka-ken			JP

US-CL-CURRENT: 424/450; 264/4.3, 264/4.32, 424/533, 428/402.2, 514/6, 514/832

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 36. Document ID: US 5676928 A

L4: Entry 36 of 44 File: USPT Oct 14, 1997

US-PAT-NO: 5676928
DOCUMENT-IDENTIFIER: US 5676928 A

TITLE: Liposomes

DATE-ISSUED: October 14, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klaveness; Jo	Oslo			NO
Berg; Arne	Sandvika			NO
Jacobsen; Trond Vegard	Oslo			NO
Rongved; Pal	Nesoddtangen			NO
Ege; Thorfinn	Tranby			NO
Kikuchi; Hiroshi	Tokyo			JP
Yachi; Kiyoto	Tokyo			JP

US-CL-CURRENT: 424/9.321; 424/450, 424/9.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 37. Document ID: US 5593622 A

L4: Entry 37 of 44 File: USPT Jan 14, 1997

US-PAT-NO: 5593622
DOCUMENT-IDENTIFIER: US 5593622 A

**** See image for Certificate of Correction ****

TITLE: Preparation of liposomes with peg-bound phospholipid on surface

DATE-ISSUED: January 14, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yoshioka; Hiroshi	Shizuoka-ken			JP
Goto; Hiroshi	Shizuoka-ken			JP

US-CL-CURRENT: 264/4.32; 264/4.3, 424/450, 428/402.2, 514/6, 514/832

38. Document ID: US 5558856 A

L4: Entry 38 of 44 File: USPT Sep 24, 1996

US-PAT-NO: 5558856
DOCUMENT-IDENTIFIER: US 5558856 A
**** See image for Certificate of Correction ****

TITLE: Microbubble-generating contrast agents for ultrasound and magnetic resonance imaging

DATE-ISSUED: September 24, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klaveness; Jo	Oslo			NL
Rongved; Pal	Hellvik			NL
Stubberud; Lars	Sodertalje			NL

US-CL-CURRENT: 424/9.37; 424/9.51, 424/9.52

39. Document ID: US 5389378 A

L4: Entry 39 of 44 File: USPT Feb 14, 1995

US-PAT-NO: 5389378
DOCUMENT-IDENTIFIER: US 5389378 A

TITLE: Benzoporphyrin vesicles and their use in photodynamic therapy

DATE-ISSUED: February 14, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Madden; Thomas D.	Vancouver			CA

US-CL-CURRENT: 424/450; 428/402.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 40. Document ID: US 5178875 A

L4: Entry 40 of 44 File: USPT Jan 12, 1993

US-PAT-NO: 5178875
DOCUMENT-IDENTIFIER: US 5178875 A
** See image for Certificate of Correction **

TITLE: Liposomal-polyene preliposomal powder and method for its preparation

DATE-ISSUED: January 12, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lenk; Robert P.	New Waverly	TX		
Mehta; Reeta	Houston	TX		
Lopez-Berestein; Gabriel	Houston	TX		

US-CL-CURRENT: 424/450; 264/4.1, 428/402.2, 428/402.21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 41. Document ID: US 5100662 A

L4: Entry 41 of 44 File: USPT Mar 31, 1992

US-PAT-NO: 5100662
DOCUMENT-IDENTIFIER: US 5100662 A

TITLE: Steroidal liposomes exhibiting enhanced stability

DATE-ISSUED: March 31, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bolcsak; Lois E.	Lawrenceville	NJ		
Boni; Lawrence	Monmouth Junction	NJ		
Popescu; Mircea C.	Plainsboro	NJ		
Tremblay; Paul A.	Hamilton	NJ		

US-CL-CURRENT: 424/450; 424/208.1, 424/210.1, 424/211.1, 424/226.1, 424/227.1, 424/228.1, 424/250.1, 424/272.1, 424/277.1, 424/283.1, 424/85.2, 428/402.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 42. Document ID: US 5049388 A

L4: Entry 42 of 44 File: USPT Sep 17, 1991

US-PAT-NO: 5049388
DOCUMENT-IDENTIFIER: US 5049388 A
**** See image for Certificate of Correction ****

TITLE: Small particle aerosol liposome and liposome-drug combinations for medical use

DATE-ISSUED: September 17, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Knight; Jack V.	Houston	TX		
Gilbert; Brian E.	Houston	TX		
Wilson; Samuel Z.	Houston	TX		
Six; Howard R.	East Stroudsborg	PA		
Wyde; Philip R.	Houston	TX		

US-CL-CURRENT: 424/450; 264/4, 264/4.1, 424/43, 428/402.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 43. Document ID: US 4970074 A

L4: Entry 43 of 44 File: USPT Nov 13, 1990

US-PAT-NO: 4970074
DOCUMENT-IDENTIFIER: US 4970074 A

TITLE: Fluorophores for encapsulation into liposomes

DATE-ISSUED: November 13, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fiechtner; Michael D.	Highland Park	IL		
Bieniarz; Christopher	Highland Park	IL		
Shipchandler; Mohamed	Libertyville	IL		
Adamczyk; Maciej	Lindenhurst	IL		

US-CL-CURRENT: 424/450; 536/53, 544/300, 549/223, 549/403, 558/8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 44. Document ID: US 4311712 A

L4: Entry 44 of 44 File: USPT Jan 19, 1982

US-PAT-NO: 4311712
DOCUMENT-IDENTIFIER: US 4311712 A

TITLE: Process for preparing freeze-dried liposome compositions

DATE-ISSUED: January 19, 1982

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Evans; John R.	Macclesfield			GB2
Fildes; Francis J. T.	Macclesfield			GB2
Oliver; Jean E.	Macclesfield			GB2

US-CL-CURRENT: 514/773; 264/4.1, 424/450, 514/181

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L3	L2 and 424/$ccls.	0	L3
L2	L1 and liposome	94	L2
L1	(solvent adj2 remov$) adj3 (lyophili$ or freezedr)	574	L1

END OF SEARCH HISTORY

L4: Entry 33 of 44 File: USPT Dec 23, 1997

DOCUMENT-IDENTIFIER: US 5700482 A
TITLE: Process for the preparation of a liposome dispersion under elevated pressure contents

Abstract Text (1):
The invention relates to a novel, advantageous process for the preparation of liposomes for the inclusion of water-soluble or hydrophilic substances or mixtures of substances, which process provides the surprising advantage, in comparison with known processes, that the proportion of substances or mixtures of substances actually included is increased and which, when used pharmaceutically, provides the advantage of sterile working conditions. In this process, a mixture consisting of at least one phospholipid and customary lipophilic excipients is subjected to a mobile carrier phase consisting of carbon dioxide and a polar organic solvent (modifier) under supercritical pressure and temperature conditions, the compressed mixed phase is reduced to normal pressure and transferred to an aqueous phase comprising a substance having water-soluble or hydrophilic properties for encapsulation in liposomes.

Brief Summary Text (1):
The present invention relates to a novel, advantageous process for the preparation of a liposome dispersion.

Brief Summary Text (2):
Liposome dispersions comprising various inclusion compounds and phospholipids, such as lecithin, have been described in numerous publications and have already been tested clinically. In order to illustrate the prior art, European Patent Application (hereinafter referred to as EP-A) 178 624 is mentioned, in which there is described a liposome dispersion comprising synthetic, purified sodium 1,2-di(9-cis-octadecenoyl)-3-sn-phosphatidyl S-serine and 1-n-hexadecanoyl-2-(9-cis-octadecenoyl)-3-sn-phosphatidyl choline as phospholipids and lipophilic N-acetyl-D-muramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1,2-dipalmitoyl-s n-glycero-3-hydroxyphosphoryloxy)-ethylamide or hydrophilic doxorubicin as encapsulated active ingredients. Those dispersions may be administered intravenously inter alia.

Brief Summary Text (3):
Liposome dispersions comprising inclusion compounds without actual pharmacological properties, such as zinc-phthalocyanine, radioactive labelling compounds or fluorescent compounds, are also known. EP-A-451 103 is mentioned by way of illustration, in which there is described a liposome dispersion comprising zinc-phthalocyanine which, following intravenous administration, may be used in so-called photodynamic chemotherapy only when stimulated with focused light (LASER).

Brief Summary Text (4):
Numerous processes for the preparation of liposome dispersions are described in the literature, for example treatment of an aqueous phospholipid dispersion with ultrasonic waves; dispersion of phospholipids with surfactants in aqueous phase and removal of the surfactants by dialysis; dissolution of phospholipids in organic solvents, removal of the solvent by lyophilisation and dispersion of the residue in aqueous phase; infusion methods or reverse phase evaporation.

Brief Summary Text (5):
Many known preparation processes are disadvantageous since only a fraction of the amount of phospholipids used forms liposomes, and those liposomes likewise comprise only a fraction of inclusion compound. In addition, mixed micelles, gel structures and double-layer aggregates of indefinable size may also be formed. Also known are stability problems, greatly varying liposome size distribution, a lack of reproducibility of the processes themselves, high residual amounts of organic solvents, residual amounts of surfactants, etc.

Brief Summary Text (6):
Furthermore, a common feature of all the preparation processes hitherto known is that only a small proportion of the substance or mixture of substances to be encapsulated is actually encapsulated in the double-layer membrane or in the interior space of the liposomes. The amount of active ingredient that is encapsulated can be increased by selecting a lipophilic substance or mixture of substances. However, if water-soluble or hydrophilic substances are to be encapsulated, the proportion of encapsulated substances always remains low in comparison with the total amount used. Water-soluble or hydrophilic substances are less prone to be enriched from the aqueous phase in a lipid phase. Moreover, lipid membranes have poor stability. When they are leaking, the aqueous contents of the interior space of the liposomes are replaced by the aqueous phase surrounding the liposomes, so that the degree of enrichment of a water-soluble active ingredient in the liposomes is being lowered.

Brief Summary Text (7):
The problem underlying the present invention is to provide a novel, improved process for the preparation of liposomes for the inclusion of water-soluble or hydrophilic substances or mixtures of substances, which process has the surprising advantage in comparison with known processes that the proportion of substances or mixtures of substances actually included is increased and which, when used pharmaceutically, provides the advantage of working conditions that are as sterile as possible.

Brief Summary Text (8):
This problem is solved by the present invention, which relates to an advantageous process for the preparation of a liposome dispersion. The liposome dispersion comprises:

Brief Summary Text (9):
a) a substance for encapsulation in liposomes or a mixture of substances for encapsulation having water-soluble or hydrophilic properties;

Brief Summary Text (15):
The process according to the present invention comprises subjecting a mixture consisting of at least one phospholipid b) and, where appropriate, lipophilic excipients d) customary for the intended application, to a mobile carrier phase consisting of carbon dioxide and a polar organic solvent (modifier) under pressure and temperature conditions which are higher than the critical pressure and the critical temperature of a pure carbon dioxide phase, reducing the compressed mixed phase that is obtainable to normal pressure and transferring it to an aqueous phase comprising a substance for encapsulation in liposomes or a mixture of substances for encapsulation a) having water-soluble or hydrophilic properties and, where appropriate, water-soluble excipients d) customary for the intended application, and, where appropriate, removing the organic solvent and/or separating off a fraction of liposomes having a desired diameter range and/or converting the liposome dispersion into a form suitable for the intended application.

Brief Summary Text (16):
In an especially preferred process variant, the phospholipid 1-n-hexadecanoyl-2-(9-cis-octadecenoyl)-3-sn-phosphatidyl choline (POPC) with the lipophilic excipient

cholesterol is subjected to a mobile carrier phase consisting of carbon dioxide with approximately from 5 to 7% ethanol as modifier, above the critical pressure and critical temperature of a pure CO.sub.2 phase (.gtoreq.72 bar, .gtoreq.32.degree. C.). After the compressed mixed phase has been reduced to normal pressure, an aqueous component comprising a water-soluble active ingredient, such as EDATREXATE (10-EDAM), is added thereto, whereupon liposomes comprising a high proportion of that water-soluble inclusion compound form spontaneously.

Brief Summary Text (18):
The expression: A substance for encapsulation in liposomes or a mixture of substances for encapsulation having water-soluble or hydrophilic properties--defines hydrophilic or water-soluble substances and mixtures of substances of the prior art which are known to be capable of inclusion in liposomes having phospholipid double layers.

Brief Summary Text (19):
Liposomes have been described in the literature in numerous publications. Their construction and their use are the subject of many studies. A distinction is made between unilamellar liposomes having one double layer and multilamellar liposomes having several double layers of phospholipids arranged in the manner of an onion skin. The size of the liposomes varies from approximately 1.0.times.10.sup.-8 to approximately 1.0.times.10.sup.-5 m.

Brief Summary Text (20):
The therapeutic use of liposomes as carriers especially of lipophilic pharmaceutical active ingredients is known. Liposomes have also been proposed as carriers of other lipophilic substances having biological activity, such as proteins, for example antibodies or enzymes, hormones, vitamins or genes, or, for analytical purposes, as carriers of labelled compounds.

Brief Summary Text (21):
Liposomes and their preparation are described in the synoptical work by Gregoriadis G. (ed.) Liposome Technology, Vol. II, Incorporation of Drugs, Proteins and Genetic Material, CRC Press 1984.

Brief Summary Text (22):
In the case of the substance or mixture of substances for encapsulation in liposomes, a distinction is made between its hydrophilic properties and its water-soluble properties. The hydrophilic property of a substance or mixture of substances is understood as meaning its tendency to build up in the phase interface of water, which is also known in the case of surfactants. This requires the presence of so-called hydrophilic groups in the molecular structure of the substance or mixture of substances in question, which groups are able to interact with water in the sense of attraction.

Brief Summary Text (27):
Instead of a pharmaceutical active ingredient or an active ingredient combination, the liposome dispersion may also comprise other substances for encapsulation, such as radio-active labelling compounds or fluorescent compounds.

Brief Summary Text (45):
Component c)--water in the required purity for the intended application--is present in the liposome dispersion in the degree of purity prescribed for the particular use, the water having been rendered germ- and pyrogen-free, for example, in accordance with the provisions of the national pharmacopoeias. For example, water for injection purposes or sterilised water for injection purposes is used.

Brief Summary Text (46):
In addition, the liposome dispersion may comprise further excipients d) that are necessary, for example, for the establishment of isotonic conditions, for example

ionic additives, such as sodium chloride, or non-ionic additives (structure formers), such as sorbitol, mannitol or glucose, or water-soluble stabilisers for the liposome dispersion, such as lactose, fructose or sucrose. In particular, the liposome dispersion comprises those additives, for example sodium chloride or mannitol, in the prescribed amounts necessary for the establishment of isotonic conditions in the injection solutions. In an especially preferred embodiment of the process, the liposome dispersion is prepared with the lipophilic excipient cholesterol. That excipient is added with the mentioned phospholipids to the mobile carrier phase consisting of CO.sub.2 and the modifier ethanol. When that mixed phase is reduced to normal pressure, liposomes form in the aqueous phase and wherein the excipient cholesterol is incorporated in the double layers consisting of phospholipids. Liposomes having cholesterol in the double layer are distinguished by increased stability.

Brief Summary Text (47):
In addition to the water-soluble excipients, the liposome dispersion may comprise further excipients that can be used for liquid pharmaceutical formulations, which excipients increase the water-solubility of the mentioned active ingredients, for example emulsifiers, wetting agents or surfactants, especially emulsifiers such as oleic acid, non-ionic surfacants of the fatty acid polyhydroxy alcohol ester type, such as sorbitan monolaurate, monooleate, monostearate or monopalmitate, sorbitan tristearate or trioleate, polyoxyethylene adducts of fatty acid polyhydroxy alcohol esters, such as polyoxyethylene sorbitan monolaurate, monooleate, monostearate, monopalmitate, tristearate or trioleate, polyethylene glycol fatty acid esters, such as polyoxyethyl stearate, polyethyleneglycol400 stearate, polyethylene glycol 2000 stearate, especially ethylene oxide/propylene oxide block polymers of the Pluronic.RTM. type (Wyandotte Chem. Corp.) or the Synperonic.RTM. type (ICI).

Brief Summary Text (48):
The advantage of the process is that a large amount of a water-soluble substance, especially of a water-soluble pharmaceutical active ingredient, such as EDATREXATE (10-EDAM), doxorubicin, cytarabine or trifosamide, can be encapsulated in liposomes. The preparation processes hitherto known are disadvantageous for water-soluble inclusion compounds since only small amounts are encapsulated in liposomes, while most of the compound remains in solution in the aqueous phase.

Brief Summary Text (49):
There are used as phospholipid preferably the above-mentioned natural or synthetic, substantially pure derivatives of lecithin, especially 1-n-hexadecanoyl-2-(9-cis-octadecenoyl)-3-sn-phosphatidyl choline (POPC). Cholesterol is preferably used as the customary lipophilic excipient. The incorporation of that excipient, which is also present in stable, natural membranes, yields liposomes having an especially stable structure, which remain stable to storage for up to several months.

Brief Summary Text (53):
The size of the liposomes formed in the aqueous phase is dependent upon various conditions, for example the composition of the mobile carrier phase, the amount of active ingredient and the lipid components, the mixing ratio thereof and the concentration in the aqueous dispersion, selection of pressure and temperature conditions, the rate of flow or variation in mixer types or capillary geometry, for example the length and diameter of the depressurisation capillary in the apparatus used for the process.

Brief Summary Text (56):
It is possible to obtain an especially uniform size distribution of the liposomes by after-treatment of the liposome dispersion, for example by treatment with ultrasonic waves or extrusion through straight-pored filters (e.g. Nucleopore.RTM.).

Brief Summary Text (57):

The separation and isolation of a fraction of large liposomes from a fraction containing small liposomes, insofar as it is at all necessary, is likewise effected by means of conventional separation methods, for example gel filtration or ultrafiltration, for example with Sepharose.RTM. 4B or Sephacryl.RTM. (Pharmacia SE) as carrier, or by sedimentation of the liposomes in an ultracentrifuge, for example with a gravitational field of 160,000.times.g. For example, after centrifugation for several hours, for example about 3 hours, in that gravitational field, liposomes are deposited, whereas small liposomes remain in dispersion and can be decanted. Repeated centrifugation results in complete separation of the large liposomes from the small liposomes.

Brief Summary Text (58):
Gel filtration especially can be used to separate off all the liposomes present in the aqueous phase having a diameter of more than about 6.0.times.10.sup.-8 m and also non-encapsulated components and excess, dispersed lipids that are present in high molecular weight aggregates and thus to produce an aqueous dispersion having a fraction of liposomes of relatively uniform size.

Brief Summary Text (59):
The completed formation of liposomes and their size distribution in the aqueous phase can be demonstrated in a manner known per se by various physical measuring methods, for example with freeze fracture samples and thin sections under an electron microscope or by X-ray diffraction, by dynamic light scattering, by mass determination of the filtrate in an analytical ultracentrifuge and especially by spectroscopy, for example in the nuclear magnetic resonance spectrum (.sup.1 H, .sup.13 C and .sup.31 P).

Brief Summary Text (60):
The liposome dispersion may be administered directly after removal of organic solvents, or it may be converted by freeze-drying into a lyophilisate, which is reconstituted immediately before administration by the addition of water in the required injection volume.

Detailed Description Text (2):
The pumps 2 and 7 convey the CO.sub.2 and the modifier from the reservoirs 1 and 6 into the apparatus. The CO.sub.2 pump is preferably cooled to -10.degree. C., the CO.sub.2 having a density of approximately 1 g/ml and being easy to pump. The pump pressure safety device 3 displays the pressure of the pumps 2 and 7. The pulse damper 4 damps the pressure pulses of the pumps 2 and 7, which occur when the pump piston is retracted. The pump control 8 controls the flow and the phase mixing ratio of the two pumps 2 and 7. The static mixers 9, 20, 25, 33 have no movable parts. Mixing occurs as a result of currents in a steel tube in which several mixing elements (current breakers) are incorporated, which splits and collects the current lines. The dynamic mixer 10 has a movable part. The movement produces a turbulent current, which mixes the phases introduced. The filter 11 retains undesired foreign particles in the mobile carrier phase consisting of CO.sub.2 and modifier. The injector 12 is provided for further additions of modifier. The check valve 13 allows the mobile carrier phase to pass only in the direction A.fwdarw.B. Should the pressure in direction B fall and become less than the pressure in direction A, compressed phase is introduced until stable, equal pressure conditions prevail. The adjustable pressure safety valve 14 opens in the case of undesired overpressure. The cross piece 15 is open in all directions. The manometer 16 displays the pressure in the recycling circuit I, which is defined by the arrangement C-D-19-20-F-G-18-17-15-C, or, preferably, C-15-17-18-G-F-20-D-C. In the recycling circuit I, the compressed homogeneous mixed phase is under homogeneous conditions. The recycling pump 17 conveys the mobile carrier phase consisting of CO.sub.2 and modifier through the extraction cell 19 and the static mixer 20 in the recycling circuit I, whereupon the lipophilic constituents (phospholipid and, where appropriate, cholesterol) previously introduced into the extraction cell 19 are dissolved. The UV detector 18 displays the degree of homogenisation of the

compressed lipid-containing mixed phase with the lipophilic constituents introduced into the extraction cell 19. The detector signal is recorded on a plotter. The extraction cell 19 is a pressure-stable steel tube with threaded connectors and filters at the inlet and outlet. Emptied chromatographic columns may also be used for that purpose. The pressure sensor 21 measures the pressure downstream of the recycling circuit I. The pressure regulator 22 comprises a piezo crystal, which is controlled by the piezo driver 23 and thus establishes the required pressure conditions. The piezo driver 23 automatically establishes the required pressure independently of the flow conditions. In the arrangement 24a,b-30a,b-31a,b-32a,b water soluble or hydrophilic substance may be added to the system which are to be encapsulated in liposomes. The arrangement 24b-30b-31b-32b in the low pressure range is preferred. The addition in arrangement 24a-30a-31a-32a is also possible. The static mixer 25 serves as a homogeniser in the formation of liposomes. The recycling pump 27 conveys the aqueous phase from the collecting vessel 26 through the static mixer 33 into the recycling circuit II, which is defined by the arrangement 29-34-26-27-29. In that circuit, uncontrolled foam formation on depressurisation of the mixed phase is prevented and homogeneity of the depressurised mixed phase is established. The water bath 28 ensures that temperature conditions in the recycling circuit I, in the pump head of the recycling pump 17 and in the detection cell 18 are constant. The three-way taps A,C,D,F,G,I,J,L,N allow the currents of the compressed phase to pass through (one outer always open) or distribute them in two directions (two outlets open). The two-way taps B,E,H,K,M,O allow the currents to flow through or prevent them from passing.

Detailed Description Text (10):
.eta.) The compressed mixed phase comprising phospholipids and cholesterol is decompressed out of the recycling circuit I through the pressure regulator 22. The mixed phase is released from 24b into the aqueous phase containing the hydrophilic or water soluble substance, whereupon liposomes form spontaneously.

Detailed Description Text (11):
.nu.) The aqueous liposome dispersion is diluted and homogenised in the recycling circuit II consisting of the arrangement 29-34-26-27-29.

Detailed Description Text (12):
.iota.) When the UV absorption has reached the original level of the mobile carrier phase (no noticeable absorption for phospholipids) and corresponds to the absorption in process step .gamma.), the experiment is concluded and the liposome suspension is analysed qualitatively and quantitatively by HPLC. A portion of the suspension is examined under a light-optical microscope.

Detailed Description Text (35):
Analysis by means of HPLC shows no decomposition products in the liposome suspension. POPC and cholesterol are not being denatured during the liposome formation process. The following mounts were found in the liposome dispersion that is obtainable:

Detailed Description Text (60):
The process is carried out analogously to Example 1 under the conditions described therein. Analysis by means of HPLC shows no decomposition products in the liposome dispersion. POPC, cholesterol and zinc-phthalocyanine tetrasulfonate are not denatured during the liposome formation process. Before gel filtration, the following amounts were found in the liposome dispersion that is obtainable:

Detailed Description Text (66):
1.0 ml of tiposome dispersion (1.03 mg of cholesterol and 5.78 mg of POPC) are gel-filtered in order to remove ZnPc(SO.sub.3 H).sub.4 that has not been included. The following mounts are found in the fractions with liposomes:

Detailed Description Text (72):
3.6 .mu.g, of which 2.6 .mu.g in liposomes.

Current US Original Classification (1):
424/450

CLAIMS:

1. A process for the preparation of a liposome dispersion comprising

subjecting at least one phospholipid of the formula ##STR2## wherein R.sub.1 is C.sub.10-20 acyl,

R.sub.2 is hydrogen or C.sub.10-20 acyl, and

R.sub.3 is hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, C.sub.1-4 alkyl, C.sub.1-5 alkyl substituted by carboxy, C.sub.2-5 alkyl substituted by hydroxy, C.sub.2-5 alkyl substituted by carboxy and by hydroxy, or C.sub.2-5 alkyl substituted by carboxy and by amino, or a salt of such phospholipid to a mobile carrier phase consisting of carbon dioxide and a polar organic solvent under pressure and temperature conditions which are higher than the critical pressure and the critical temperature of a pure carbon dioxide phase, reducing the compressed mixed phase that is obtainable to normal pressure and transferring it to an aqueous phase comprising water in the purity required for the intended application and a non-proteinaceous substance or a mixture of non-proteinaceous substances having water-soluble or hydrophilic properties for encapsulation in liposomes and removing the organic solvent and/or separating off a fraction of liposomes having a desired diameter range and/or converting the liposome dispersion into a form suitable for the intended application.

7. A process according to claim 1, wherein the liposome composition further comprises cholesterol.

8. A process according to claim 1, wherein the liposome composition further comprises at least one water-soluble excipient for the establishment of isotonic conditions.

14. A process according to claim 1, wherein the liposome dispersion that is obtainable is convened into a lyophilisate which is then reconstituted by the addition of water in the required injection volume.

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L4: Entry 30 of 44 File: USPT Oct 27, 1998

DOCUMENT-IDENTIFIER: US 5827502 A
TITLE: Microparticulate microbubble-generating contrast agents

Detailed Description Text (14):
In an alternative method according to the invention a (preferably aqueous) solution of the carbohydrate is mixed with a liposome-forming material (e.g. a thin film of a lipid such as lecithin formed on the inner surface of the mixing vessel by evaporating the solvent from a solution of the lipid in an appropriate organic solvent, for example a chlorinated hydrocarbon such as chloroform) so as to form a liposome-containing carbohydrate solution from which the solvent may be removed (e.g. by freeze-drying) to yield a product comprising carbohydrate-containing liposomes; this product may be micronised to given microparticles of the desired size.

Detailed Description Text (34):
Freeze-dried Liposomes Containing D-(+)-galactose Particles

Detailed Description Text (35):
1 ml 100 mg/ml phosphatidylcholine was dissolved in 10 ml chloroform. The mixture was poured into a round bottom flask, and the organic phase was evaporated at 40.degree. C. in such a way that a thin film of the phosphatidylcholine was formed on the inner surface of the flask. 10 ml of a sterile, pyrogen free 40% aqueous D-(+)-galactose solution was then added at 40.degree. C. and the flask was kept rotating for 1 hour. The aqueous solution containing liposomes and dissolved galactose was then freeze-dried for 24 hours, and the resulting product consisting of freeze-dried galactose and freeze-dried galactose-filled liposomes was then ground in a ball-mill to yield a product with a particle size distribution of 1-20 .mu.m.

Current US Original Classification (1):
424/9.52

Current US Cross Reference Classification (1):
424/9.37

Current US Cross Reference Classification (2):
424/9.51

CLAIMS:

34. A process for preparing a contrast agent as claimed in claim 1 which comprises (i) either mixing solutions of the carbohydrate and surfactant and removing the solvent(s) therefrom or mixing a solution of the carbohydrate with a liposome-forming material and removing the solvent therefrom and (ii) micronising the resulting mixture to yield the desired microparticles.

L4: Entry 29 of 44 File: USPT Nov 3, 1998

DOCUMENT-IDENTIFIER: US 5830498 A
TITLE: Liposomal-polyene preliposomal powder and method for its preparation

Abstract Text (1):
A method is disclosed for preparing a stable preliposomal powder which, when reconstituted with water or saline solution, forms a suspension of liposomes containing a polyene drug, such as nystatin. The method involves the steps of combining at least one phospholipid with a first organic solvent to form a first solution, adding a clarifying amount of water to the first solution, combining a polyene with a second organic solvent to form a second solution, combining the first and second solutions to produce a substantially clear combined solution, and then removing the organic solvents, leaving a powder.

Brief Summary Text (4):
Some of the inventors of this patent previously discovered that these problems could be overcome by formulating nystatin in phospholipid vesicles, or liposomes. Such a liposomal formulation is considerably less toxic to the animal to which it is administered, but is still effective against fungal infection, and therefore is suitable for systemic use. U.S. Pat. No. 4,812,312 discloses that invention, and is incorporated here by reference.

Brief Summary Text (5):
One drawback to some liposomal drug formulations is their less-than-desirable shelf life. Another drawback is the relative complexity of the process needed to prepare them. In view of these drawbacks, it would be highly desirable to produce a stable, dry formulation which could be rehydrated when needed for treatment of a patient. Lyophilized, or freeze-dried, powders are a possible answer to this need. However, in order to be practical, a lyophilized powder must not only be stable and capable of reconstituting as liposomes, it must capable of being prepared by a process that is simple and inexpensive enough so that it will be practical and cost-effective for commercial use.

Brief Summary Text (8):
The present invention generally concerns a method for producing a powder suitable for the preparation of polyene-containing liposomes upon suspension in an aqueous solution. In one aspect, the present invention relates to a method of preparing a liposomal-polyene preliposomal powder, comprising the steps of combining at least one phospholipid with a first organic solvent to form a first solution; combining the first solution with a clarifying amount of water, forming a clarified first solution; combining polyene with a second organic solvent to form a second solution; combining the clarified first solution and the second solution to produce a substantially clear combined solution; and removing substantially all the solvent from the combined solution. In a preferred embodiment of this aspect of the present invention, a method of preparing a liposomal-nystatin preliposomal powder comprises the steps of combining dimyristoyl phosphatidyl choline and dimyristoyl phosphatidyl glycerol with t-butyl alcohol to form a first solution; combining the first solution with a clarifying amount of water, forming a clarified first solution; combining nystatin with dimethyl sulfoxide to form a second solution; combining the clarified first solution and the second solution to produce a substantially clear combined solution; and removing substantially all the t-butyl

alcohol and dimethyl sulfoxide from the combined solution.

Brief Summary Text (15):
The present invention facilitates the formulation and reconstitution of liposomal-polyene from a degradation-resistant preliposomal powder. The simplicity of the present invention makes it suitable for large-scale manufacturing. Further, it produces a stable powder which can be easily stored for at least one year. In addition, when reconstituted, the product of the present method forms multilamellar liposomes which have a mean size that is suitable for administration to humans, for example in the systemic administration of liposomal nystatin to treat a fungal or viral infection.

Detailed Description Text (2):
A method in accordance with the present invention can include the following steps. First, one or more phospholipids are combined with a first organic solvent. The phospholipids which can be used are those which are suitable for the preparation of liposomes, and are well-known to those skilled in the art. Two specific examples that are particularly preferred in the present invention are dimyristoyl phosphatidyl choline and dimyristoyl phosphatidyl glycerol. The preferred weight ratio of DMPC:DMPG is approximately 7:3. Suitable organic solvents for use as the first organic solvent include t-butyl alcohol. The ratio of phospholipid to first organic solvent is preferably between about 10 g:160 cc and about 10 g:640 cc, and is most preferably about 10 g:320 cc. The combination of phospholipid and first organic solvent creates a first solution.

Detailed Description Text (6):
The clarified first solution is then combined with the second solution to produce a substantially clear combined solution. Preferably, the concentration of nystatin in the combined solution is about 2.5-2.75 mg/ml and the concentration of phospholipid is about 25-27.5 mg/ml. The ratio of solids to liquid in this solution is believed to be important to the ready reconstitution of the preliposomal powder into liposomes when water is added. If the solids concentration is too high, the resultant dry product is denser than optimal and does not perform as well as desired on reconstitution.

Detailed Description Text (7):
Next, substantially all of the organic solvents are removed from the combined solution, for example by lyophilization, producing a preliposomal powder. The powder can be reconstituted into an aqueous formulation of liposomal polyene by adding a pharmaceutically acceptable solvent, such as water or saline solution.

Detailed Description Text (13):
The formulation is reconstituted by adding about 50 cc of water to the powder for every 1 g of polyene. It is preferred to heat the solution above 27.degree. C., most preferably between about 30.degree. and 45.degree. C. for about 15-60 minutes, to aid the hydration process. The powder initially disperses into clumps several tens of .mu. in diameter. When the solution is warmed, the clumps hydrate and spontaneously form liposomes. The temperature at which this transition occurs may be due to the phase transition temperature of the lipids, which for the above-described materials is around 23.degree. C.

Detailed Description Text (14):
After reconstitution, the mean particle size is about 2-3 .mu.M, with not more than 1% having a diameter over 8 .mu.M. The incorporation efficiency of drug in liposomes is greater than 90%, and may approach 100%.

Current US Original Classification (1):
424/450

CLAIMS:

4. A method of preparing a halogen-free reconstituted polyene-liposomal solution having a mean particle size of 2-3 .mu.m, with not more than 1% of the liposomes having a diameter over 8 .mu.m by the process of

(i) preparing a liposomal-polyene preliposomal powder prepared by a method comprising the steps of:

a. combining at least one phospholipid with a first halogen free organic solvent to form a first solution;

b. combining the first solution with a clarifying amount of water, forming a clarified first solution;

c. combining polyene with a second halogen free organic solvent to form a second solution;

d. combining the clarified first solution and the second solution to produce a substantially clear combined solution; and

e. removing substantially all the solvent from the combined solution by initial freeze-drying at about -45.degree. C. at a vacuum of no more than 200 microns Hg and increasing said temperature by approximately 2.3.degree. C./hour to 10.degree. C; and

(ii) adding a pharmaceutically acceptable solvent to the preliposomal powder.

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☐ 1. Document ID: US 6844004 B2

L4: Entry 1 of 44 File: USPT Jan 18, 2005

US-PAT-NO: 6844004
DOCUMENT-IDENTIFIER: US 6844004 B2

TITLE: Topical formulations of natamycin/pimaricin

DATE-ISSUED: January 18, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Andersson; Borje S.	Houston	TX		

US-CL-CURRENT: 424/405; 424/400, 424/70.1, 514/31

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Drawi De

☐ 2. Document ID: US 6787153 B1

L4: Entry 2 of 44 File: USPT Sep 7, 2004

US-PAT-NO: 6787153
DOCUMENT-IDENTIFIER: US 6787153 B1

TITLE: Human monoclonal antibody specifically binding to surface antigen of cancer cell membrane

DATE-ISSUED: September 7, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Hirakawa; Yoko	Yokohama			JP
Ito; Norihiko	Yokohama			JP
Nagaike; Kazuhiro	Sagamihara			JP

US-CL-CURRENT: 424/450; 424/133.1, 424/134.1, 424/138.1, 424/142.1, 424/155.1, 424/174.1, 530/387.1, 530/387.7, 530/388.15, 530/388.8, 530/389.7, 530/391.1, 530/391.7, 530/865, 530/866, 530/867

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D.

☐ 3. Document ID: US 6696081 B2

L4: Entry 3 of 44 File: USPT Feb 24, 2004

US-PAT-NO: 6696081
DOCUMENT-IDENTIFIER: US 6696081 B2

TITLE: Carbohydrate based lipid compositions and supramolecular structures comprising same

DATE-ISSUED: February 24, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Hird; Geoffrey S.	Durham	NC		

US-CL-CURRENT: 424/450; 514/23, 514/25, 514/44, 536/117, 536/18.7, 548/413, 549/6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 4. Document ID: US 6677300 B1

L4: Entry 4 of 44 File: USPT Jan 13, 2004

US-PAT-NO: 6677300
DOCUMENT-IDENTIFIER: US 6677300 B1

TITLE: Treatment of microvascular angiopathies

DATE-ISSUED: January 13, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schreiner; George F.	Los Altos Hills	CA		
Johnson; Richard J.	Seattle	WA		

US-CL-CURRENT: 514/2; 424/198.1, 435/455, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 5. Document ID: US 6593294 B1

L4: Entry 5 of 44 File: USPT Jul 15, 2003

US-PAT-NO: 6593294

DOCUMENT-IDENTIFIER: US 6593294 B1

TITLE: Pharmaceutical composition comprising Factor VIII and neutral liposomes

DATE-ISSUED: July 15, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Baru; Moshe	Pardes Hana			IL
Bar; Liliana	Rehovot			IL
Nur; Israel	Moshav			IL

US-CL-CURRENT: 514/2; 424/450, 514/802, 514/834, 530/350, 530/380, 530/383

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 6. Document ID: US 6589782 B1

L4: Entry 6 of 44 File: USPT Jul 8, 2003

US-PAT-NO: 6589782
DOCUMENT-IDENTIFIER: US 6589782 B1

TITLE: Angiogenic factor and use thereof in treating cardiovascular disease

DATE-ISSUED: July 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Neufeld; Gera	Haifa			IL
Keshet; Eli	Kiryet Lam			IL
Vlodavsky; Israel	Meraseret Zion			IL
Poltorak; Zoya	Jerusalem			IL

US-CL-CURRENT: 435/320.1; 424/93.2, 424/93.21, 435/325, 435/455, 514/44, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 7. Document ID: US 6517860 B1

L4: Entry 7 of 44 File: USPT Feb 11, 2003

US-PAT-NO: 6517860
DOCUMENT-IDENTIFIER: US 6517860 B1
**** See image for Certificate of Correction ****

TITLE: Methods and compositions for improved bioavailability of bioactive agents for mucosal delivery

DATE-ISSUED: February 11, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Roser; Bruce J.	Cambridge			GB
Sanderson; Ian	Hertfordshire			GB
Kampinga; Jaap	Groningen			NL
Colaco; Camilo	Cambridge			GB

US-CL-CURRENT: 424/434; 424/45, 424/450, 514/53, 514/958, 536/119

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw D

☐ 8. Document ID: US 6475796 B1

L4: Entry 8 of 44 File: USPT Nov 5, 2002

US-PAT-NO: 6475796
DOCUMENT-IDENTIFIER: US 6475796 B1

TITLE: Vascular endothelial growth factor variants

DATE-ISSUED: November 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pollitt; N. Stephen	Los Altos	CA		
Abraham; Judith A.	San Jose	CA		

US-CL-CURRENT: 435/455; 424/198.1, 514/2, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw D

☐ 9. Document ID: US 6461637 B1

L4: Entry 9 of 44 File: USPT Oct 8, 2002

US-PAT-NO: 6461637
DOCUMENT-IDENTIFIER: US 6461637 B1

TITLE: Method of administering liposomal encapsulated taxane

DATE-ISSUED: October 8, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rahman; Aquilur	Long Grove	IL		

US-CL-CURRENT: 424/450; 514/449, 514/510

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw D

☐ 10. Document ID: US 6368619 B1

L4: Entry 10 of 44 File: USPT Apr 9, 2002

US-PAT-NO: 6368619
DOCUMENT-IDENTIFIER: US 6368619 B1

TITLE: Hydrophobic preparations of hydrophilic species and process for their preparation

DATE-ISSUED: April 9, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
New; Roger Randal Charles	London			GB
Kirby; Christopher John	Berkshire			GB

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 424/812, 424/94.3, 514/2, 514/21, 514/3, 514/44, 514/6, 514/8, 514/937

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 11. Document ID: US 6352722 B1

L4: Entry 11 of 44 File: USPT Mar 5, 2002

US-PAT-NO: 6352722
DOCUMENT-IDENTIFIER: US 6352722 B1

TITLE: Derivatized carbohydrates, compositions comprised thereof and methods of use thereof

DATE-ISSUED: March 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Blair; Julian A.	St. Ives			GB

US-CL-CURRENT: 424/484; 424/464, 424/469, 424/488, 514/178

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 12. Document ID: US 6284282 B1

L4: Entry 12 of 44 File: USPT Sep 4, 2001

US-PAT-NO: 6284282
DOCUMENT-IDENTIFIER: US 6284282 B1

TITLE: Method of spray freeze drying proteins for pharmaceutical administration

DATE-ISSUED: September 4, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Maa; Yuh-Fun	Millbrae	CA		
Nguyen; Phuong-Anh	San Mateo	CA		

US-CL-CURRENT: 424/499; 424/45, 424/46, 424/489, 514/12, 514/13, 514/2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. D

☐ 13. Document ID: US 6245358 B1

L4: Entry 13 of 44 File: USPT Jun 12, 2001

US-PAT-NO: 6245358
DOCUMENT-IDENTIFIER: US 6245358 B1

TITLE: Pharmaceutical compositions containing polymer derivative-bound anthracycline glycosides and a method for their preparation

DATE-ISSUED: June 12, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Adami; Marco	Milan			IT
Magrini; Roberto	Milan			IT
Maranghi; Paolo	Milan			IT
Suarato; Antonino	Milan			IT

US-CL-CURRENT: 424/486; 424/423

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. D

☐ 14. Document ID: US 6217886 B1

L4: Entry 14 of 44 File: USPT Apr 17, 2001

US-PAT-NO: 6217886
DOCUMENT-IDENTIFIER: US 6217886 B1

TITLE: Materials and methods for making improved micelle compositions

DATE-ISSUED: April 17, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Onyuksel; Hayat	Western Springs	IL		

Rubinstein; Israel Highland Park IL

US-CL-CURRENT: 424/401; 264/4.1, 264/4.3, 264/4.6, 424/1.21, 424/450, 424/9.321, 424/9.51, 514/2, 514/21, 514/937

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 15. Document ID: US 6211228 B1

L4: Entry 15 of 44 File: USPT Apr 3, 2001

US-PAT-NO: 6211228
DOCUMENT-IDENTIFIER: US 6211228 B1

TITLE: Compositions and methods for treating mast-cell mediated conditions

DATE-ISSUED: April 3, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rice; Ken Duane	Palo Alto	CA		
Dener; Jeffrey Mark	Daly City	CA		
Gangloff; Anthony Robert	San Mateo	CA		
Kuo; Elaine Yee-Lin	San Francisco	CA		

US-CL-CURRENT: 514/450; 424/43, 424/45, 514/211.06, 514/252.1, 514/316, 514/465, 514/479, 540/575, 544/357, 546/187, 549/347, 549/434, 560/25, 560/26

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 16. Document ID: US 6156337 A

L4: Entry 16 of 44 File: USPT Dec 5, 2000

US-PAT-NO: 6156337
DOCUMENT-IDENTIFIER: US 6156337 A

TITLE: Method for high loading of vesicles with biopolymeric substances

DATE-ISSUED: December 5, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barenholz; Yechezkel	Jerusalem			IL
Nur; Israel	Tel Aviv			IL
Bar; Lilianne K.	Rehovot			IL
Diminsky; Dvorah	Jerusalem			IL
Baru; Moshe	Pardes-Hanna			IL

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 424/812, 424/94.3, 436/829

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 17. Document ID: US 6146659 A

L4: Entry 17 of 44 File: USPT Nov 14, 2000

US-PAT-NO: 6146659
DOCUMENT-IDENTIFIER: US 6146659 A

TITLE: Method of administering liposomal encapsulated taxane

DATE-ISSUED: November 14, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rahman; Aquilur	Long Grove	IL		

US-CL-CURRENT: 424/450; 514/449, 514/510

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 18. Document ID: US 6139869 A

L4: Entry 18 of 44 File: USPT Oct 31, 2000

US-PAT-NO: 6139869
DOCUMENT-IDENTIFIER: US 6139869 A
** See image for Certificate of Correction **

TITLE: Human monoclonal antibody specifically binding to surface antigen of cancer cell membrane

DATE-ISSUED: October 31, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hosokawa; Saiko	Kawasaki			JP
Tagawa; Toshiaki	Yokohama			JP
Hirakawa; Yoko	Yokohama			JP
Ito; Norihiko	Yokohama			JP
Nagaike; Kazuhiro	Sagamihara			JP

US-CL-CURRENT: 424/450; 424/138.1, 424/142.1, 424/155.1, 424/174.1, 424/812, 435/330, 435/344, 435/372.2, 530/387.7, 530/388.15, 530/388.8, 530/391.1, 530/809

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 19. Document ID: US 6132699 A

L4: Entry 19 of 44 File: USPT Oct 17, 2000

US-PAT-NO: 6132699
DOCUMENT-IDENTIFIER: US 6132699 A

TITLE: Microencapsulated fluorinated gases for use as imaging agents

DATE-ISSUED: October 17, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bernstein; Howard	Cambridge	MA		
Straub; Julie Ann	Winchester	MA		
Brush; Henry T.	Somerville	MA		
Wing; Richard E.	Cambridge	MA		

US-CL-CURRENT: 424/9.52

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 20. Document ID: US 6123923 A

L4: Entry 20 of 44 File: USPT Sep 26, 2000

US-PAT-NO: 6123923
DOCUMENT-IDENTIFIER: US 6123923 A
** See image for Certificate of Correction **

TITLE: Optoacoustic contrast agents and methods for their use

DATE-ISSUED: September 26, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Wu; Yunqiu	Tucson	AZ		

US-CL-CURRENT: 424/9.52; 424/450, 424/9.1, 424/9.2, 424/9.3, 424/9.6, 514/410

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 21. Document ID: US 6066331 A

L4: Entry 21 of 44 File: USPT May 23, 2000

US-PAT-NO: 6066331
DOCUMENT-IDENTIFIER: US 6066331 A

TITLE: Method for preparation of vesicles loaded with biological structures, biopolymers and/or oligomers

DATE-ISSUED: May 23, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barenholz; Yechezkel	Jerusalem			IL
Bar; Lilianne K.	Rehovot			IL
Diminsky; Dvorah	Jerusalem			IL
Baru; Moshe	Pardes-Hanna			IL

US-CL-CURRENT: 424/450; 424/520, 424/93.7, 424/94.1, 435/177, 435/182, 436/528, 436/535, 514/2, 514/44, 530/812, 530/817

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 22. Document ID: US 6045815 A

L4: Entry 22 of 44 File: USPT Apr 4, 2000

US-PAT-NO: 6045815
DOCUMENT-IDENTIFIER: US 6045815 A

TITLE: Parenteral pimaricin as treatment of systemic infections

DATE-ISSUED: April 4, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Andersson; Borje S.	Houston	TX		
Anaissie; Elias J.	Little Rock	AR		

US-CL-CURRENT: 424/405; 424/406, 514/31, 514/937, 514/943

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 23. Document ID: US 5997888 A

L4: Entry 23 of 44 File: USPT Dec 7, 1999

US-PAT-NO: 5997888
DOCUMENT-IDENTIFIER: US 5997888 A

TITLE: Cosmetic preparations

DATE-ISSUED: December 7, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Weder; Hans Georg	Ruschlikon	CH
Weder; Marc Antoine	Ruschlikon	CH

US-CL-CURRENT: 424/401; 514/78, 514/844, 514/846, 514/847, 514/848, 514/937, 514/938

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 24. Document ID: US 5985281 A

L4: Entry 24 of 44 File: USPT Nov 16, 1999

US-PAT-NO: 5985281
DOCUMENT-IDENTIFIER: US 5985281 A

TITLE: Chemical compounds

DATE-ISSUED: November 16, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Taylorson; Christopher John	London			GB
Eggelte; Hendrikus Johannes	Harrow			GB
Tarragona-Fiol; Antonio	London			GB
Rabin; Brian Robert	London			GB
Boyle; Francis Thomas	Macclesfield			GB
Hennam; John Frederick	Macclesfield			GB
Blakey; David Charles	Macclesfield			GB
Marsham; Peter Robert	Macclesfield			GB
Heaton; David William	Macclesfield			GB
Davies; David Huw	Macclesfield			GB
Slater; Anthony Michael	Macclesfield			GB
Hennequin; Laurent Francois Andre	Cergy Cedex			FR

US-CL-CURRENT: 424/178.1; 424/1.17, 424/182.1, 424/94.1, 435/320.1, 514/12, 530/391.1, 530/391.7, 536/23.1, 536/23.4, 562/11

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 25. Document ID: US 5968549 A

L4: Entry 25 of 44 File: USPT Oct 19, 1999

US-PAT-NO: 5968549
DOCUMENT-IDENTIFIER: US 5968549 A

TITLE: Solubilisation aids

DATE-ISSUED: October 19, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
New; Roger Randal Charles	London			GB
Kirby; Christopher John	Berkshire			GB

US-CL-CURRENT: 424/450; 264/4.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 26. Document ID: US 5965158 A

L4: Entry 26 of 44 File: USPT Oct 12, 1999

US-PAT-NO: 5965158
DOCUMENT-IDENTIFIER: US 5965158 A
**** See image for Certificate of Correction ****

TITLE: Liposomal-polyene preliposomal powder and method for its preparation

DATE-ISSUED: October 12, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Link; Robert P.	New Waverly	TX		
Mehta; Reeta	Houston	TX		
Lopez-Berestein; Gabriel	Houston	TX		

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 424/489, 424/498, 428/402.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 27. Document ID: US 5846458 A

L4: Entry 27 of 44 File: USPT Dec 8, 1998

US-PAT-NO: 5846458
DOCUMENT-IDENTIFIER: US 5846458 A
**** See image for Certificate of Correction ****

TITLE: Inhibition adsorption of proteins on the liposome surface

DATE-ISSUED: December 8, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yoshioka; Hiroshi	Shizuoka-ken			JP
Goto; Hiroshi	Shizuoka-ken			JP

US-CL-CURRENT: 264/4.32; 264/4.3, 264/4.6, 424/450, 514/832

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 28. Document ID: US 5840083 A

L4: Entry 28 of 44 File: USPT Nov 24, 1998

US-PAT-NO: 5840083
DOCUMENT-IDENTIFIER: US 5840083 A
** See image for Certificate of Correction **

TITLE: Implant device having biocompatiable membrane coating

DATE-ISSUED: November 24, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Braach-Maksvytis; Vijoleta Lucija Bronislava	New South Wales			AU

US-CL-CURRENT: 424/423; 424/422, 435/7.21, 623/8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 29. Document ID: US 5830498 A

L4: Entry 29 of 44 File: USPT Nov 3, 1998

US-PAT-NO: 5830498
DOCUMENT-IDENTIFIER: US 5830498 A

TITLE: Liposomal-polyene preliposomal powder and method for its preparation

DATE-ISSUED: November 3, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lenk; Robert P.	New Waverly	TX		
Mehta; Reeta	Houston	TX		
Lopez-Berestein; Gabriel	Houston	TX		

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 30. Document ID: US 5827502 A

L4: Entry 30 of 44 File: USPT Oct 27, 1998

US-PAT-NO: 5827502

DOCUMENT-IDENTIFIER: US 5827502 A

TITLE: Microparticulate microbubble-generating contrast agents

DATE-ISSUED: October 27, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klaveness; Jo	Oslo			NO
Rongved; Pal	Hellvik			NO
Stubberud; Lars	Sodertalje			SE

US-CL-CURRENT: 424/9.52; 424/9.37, 424/9.51

Terms	Documents
L2 and 424/$.ccls.	44